

### REMARKS

Claims 75–84 are in the case.

Claim 75 is amended herewith. Basis is found in Example XXXIV [0207] in the patent publication.

Claim 84 is a new claim; basis is submitted to be found in the patent application publication in [003] which indicates that nitroglycerin tolerance is loss of clinical sensitivity to nitroglycerin and in Background Example 4 which shows that DTT, DHLA and TCEP restore clinical sensitivity *in vitro* and [0206] and [0207] which are directed to restoring clinical sensitivity *in vivo*.

We turn now to the rejection of paragraph 6 of the Office Action which takes the position under 35 U.S.C. 112, first paragraph that the invention is enabled only for angina. Reconsideration is requested. The rejection misses that the invention is independent of the disease for which nitroglycerin is administered and is rather directed to restoring clinical sensitivity to nitroglycerin to a patient who has lost clinical sensitivity to nitroglycerin (see claims 75 and 84). In the context here nitrate tolerance means loss of clinical sensitivity to nitroglycerin (see [0003]); in other words nitroglycerin no longer works for the condition for which it is administered and the particular condition is irrelevant.

In paragraphs 7 and 8 of the Office Action, objection is made based on the second paragraph of 35 U.S.C. 112 to the expression “administering inactivated mtALDH activating effective amount of agent” as being unclear. Reconsideration is

requested.

Firstly the expression is not in new claim 84. Note also that dosage range is given in [0059] and specific dosages for DTT, DHLA and TCEP are set forth in Background Example 4 and in Figure 1.

Turning now to claim 75, it is submitted that the meaning of this is made definite by Background Example IV. Metes and bounds of dosage are given in [0059].

We turn now to the rejection of paragraph 10, i.e. the rejection of claims 75-78 and 81 under 35 U.S.C. 102(b) as anticipated by Weischer et al. DE 4420 102 A1. The rejection takes the positions that (1) a patient when treated with nitroglycerin has some degree of tolerance (relying on page 6, Table 1), (2) Weischer teaches administration of DHLA in combination with organic nitrates to treat nitrate tolerance (relying on claim 21), (3) that Weischer teaches that the combination of nitrate and DHLA shows a therapeutic anti organic nitrate tolerant effect, and (4) that administration of DHLA inherently affects mtALDH.

Reconsideration is requested.

First, we indicate what Weischer does teach. Weischer teaches that nitrate tolerance will occur on administration of nitroglycerin, and that the combination of DHLA with nitroglycerin produces a stronger/synergistic effect compared to nitroglycerin alone.

Turning now to the rejection of paragraph 10, there is no anticipation. Claims 75 and 84 don't recite "some degree of tolerance" but rather loss of clinical sensitivity to nitroglycerin, i.e. the patient no longer responds to nitroglycerin. Thus the patient in

claims 75 and 84 is different from the patient the Office Action says is inherently present in Weischer. The patient in claims 75 and 84 is one where nitroglycerin alone no longer can provide therapy. The patient in Weischer on the other hand according to the Office Action is one where nitroglycerin provides some therapy but less therapy ("some degree of tolerance"). The claims are directed to restoring clinical sensitivity to nitroglycerin to a patient who is no longer sensitive to nitroglycerin; Weischer doesn't teach administration of DHLA to this patient. Weischer's Table 1 does not teach administration to a patient who no longer responds to nitroglycerin; Table 1 rather teaches administration of organic nitrate plus DHLA to a patient with angina but not to a patient who has lost clinical sensitivity to nitroglycerin. Nor does claim 21 make up for this deficiency. The phrase "and that organic nitrate tolerance" in claim 21 doesn't make any sense and obviously some words are left out and must mean in view of the rest of Weischer that organic nitrate tolerance is delayed. Otherwise what does the word "that" mean? The phrase clearly doesn't mean treating a patient who no longer responds to nitroglycerin.

What Weischer teaches is that DHLA causes nitroglycerin to have a stronger effect, that is that DHLA potentiates the effect of nitroglycerin or causes less nitroglycerin to be necessary for the same effect. In other words according to Weischer the effect provided by DHLA can be made up for by use of more nitroglycerin. But potentiation does not mean restoring clinical sensitivity in the claimed milieu. Thus there is no obviousness position based on Weischer either.

In this regard consider N-acetylcysteine. There are a number of articles that teach that N-acetylcysteine potentiates the effect of nitroglycerin, that is makes possible the use of less nitroglycerin for the same effect. In this regard see Loscalzo, J., J. Clin. Invest. 76(2), 703-708 (8/85) for *in vitro* effect, especially Figure 1 at page 704 which shows the potentiation effect; and Horowitz, M.B. et al., Circulation 68(6), 1247-1253 (12/83) where the abstract indicates *in vivo* potentiation effect; and the abstracts of Nishikawa, Y., J. Cardiovasc. Pharmacol. 32, 21-28 (1998) and Tate, Y., et al. Heart Vessels, 13(6), 263-268 (1998). Copies of Loscalzo, Horowitz, Nishikawa and Tate are attached.

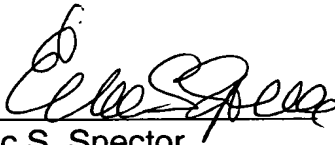
But despite potentiating the effect of nitroglycerin, N-acetylcysteine does not restore clinical sensitivity to nitroglycerin to a patient who has lost such sensitivity (no longer responds to nitroglycerin). See Figure 1 of the instant patent application and Figure 4 of TCM 16(8), 259-265, copy attached.

Thus the potentiation effect taught by Weischer cannot provide a reasonable expectation of success for the sensitivity restoration effect of the claims.

The other prior art rejections all depend on Weischer and are defective for the same reasons as Weischer and are asserted only to shown that DTT and TCEP are equivalent to DHLA. Additionally, the combination rejections are defective because the secondary references do not show equivalence of DTT and TCEP to DHLA in the instant milieu which the instant application Figure 1 indicates is something special.

Allowance is requested.

Respectfully submitted,  
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